

10/537346

Antibacterial Agents

This invention relates to novel hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity, to methods of treatment using such compounds, and to pharmaceutical and veterinary compositions comprising such compounds.

Background to the Invention

Many classes of antibacterial agents are known, including the penicillins and cephalosporins, tetracyclines, sulfonamides, monobactams, fluoroquinolones and quinolones, aminoglycosides, glycopeptides, macrolides, polymyxins, lincosamides, trimethoprim and chloramphenicol. The fundamental mechanisms of action of these antibacterial classes vary.

Bacterial resistance to many known antibacterials is a growing problem. Accordingly there is a continuing need in the art for alternative antibacterial agents, especially those which have mechanisms of action fundamentally different from the known classes, and/or which are effective against the causative organisms of community acquired respiratory infections, and/or which are selective in their pharmacological activity, thus reducing risk of unwanted side effects..

Amongst the Gram-positive pathogens, such as staphylococci, streptococci, mycobacteria and enterococci, resistant strains have evolved/arisen which makes them particularly difficult to eradicate. Examples of such strains are methicillin resistant *Staphylococcus aureus* (MRSA), methicillin resistant coagulase negative Staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiply resistant *Enterococcus faecium*

Brief Description of the Invention

This invention makes available a new class of hydroxamic acid and N-formyl hydroxylamine derivatives having antibacterial activity. The compounds are characterised inter alia by the presence of a cyclic diazole feature in their structural

backbone.

Although it may be of interest to establish the mechanism of action of the compounds with which the invention is concerned, it is their ability to inhibit bacterial growth that makes them useful. However, it is presently believed that their antibacterial activity is due, at least in part, to intracellular inhibition of bacterial polypeptide deformylase (PDF; EC 3.5.1.31).

Related Prior Art

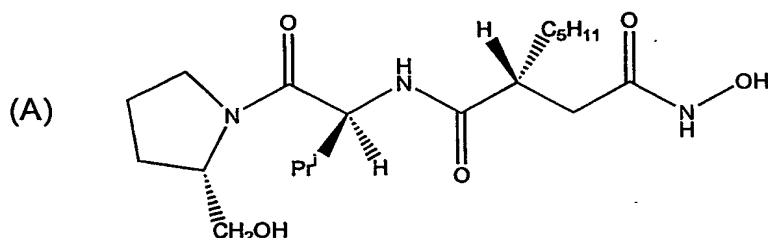
Although there are many publications disclosing both hydroxamic acid and N-formyl hydroxylamine derivatives as inhibitors of various metalloenzymes such as angiotensin converting enzyme, enkephalinase and the matrix metalloproteinases, there are relatively few relating to such compounds as antibacterial agents. The following patent publications are relevant in that connection:

WO 99/39704	(British Biotech)
WO 99/57097	(Versicor)
WO 99/59568	(British Biotech)
WO 00/35440	(British Biotech)
WO 00/44373	(British Biotech)
WO 00/58294	(British Biotech)
WO 00/61134	(British Biotech)
WO 01/10835	(British Biotech)
WO 01/38561	(Questcor)
WO 01/40198	(Aventis)
WO 01/42431	(Bayer)
WO 01/44178	(Versicor)
WO 01/44179	(Versicor)
WO 01/85160	(SmithKline Beecham)
WO 01/85170	(SmithKline Beecham)
WO 02/28829	(Questcor)
WO 02/41886	(British Biotech)

WO 02/50081 (British Biotech)

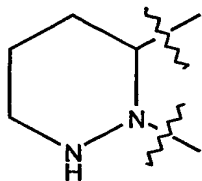
WO 02/070541 (SmithKline Beecham) relates to PDF inhibitor compounds which have a hydrazide feature in the backbone and an N-formylhydroxylamino metal binding group.

In addition the natural antibiotic actinonin (see for example J.C.S Perkin I, 1975, 819) is a hydroxamic acid derivative of Structure (A):



which is now known to act by inhibition of PDF. In addition to actinonin, various structural analogues of actinonin have also been shown to have antibacterial activity (see for example Broughton et al. (Devlin et al. Journal of the Chemical Society. Perkin Transactions 1 (9):830-841, 1975; Broughton et al. Journal of the Chemical Society. Perkin Transactions 1 (9):857-860, 1975).

The matlystatin group of compounds share a number of structural similarities with actinonin. Both are peptidic molecules with functional hydroxamic acid metal binding groups (Ogita et al., J. Antibiotics. 45(11):1723-1732; Tanzawa et al., J. Antibiotics. 45(11):1733-1737; Haruyama et al., J. Antibiotics. 47(12):1473-1480; Tamaki et al., J. Antibiotics. 47(12):1481-1492). The matlystatins and their close structural analogues are characterised by the presence in the molecule of a divalent piperazin-1, 6-diyl group, i.e.



In view of their close structural similarity to actinonin, the observation that actinonin inhibits PDF implies that matlystatin compounds may also inhibit PDF.

For a recent review of peptide deformylase inhibitors, see Clements et. al., Curr. Med. Chem. - Anti-Infective Agents, 2002, 1, 239-249.

The following patent publications disclose N-formyl hydroxylamine structures:

EP-B-0236872	(Roche)
WO 92/09563	(Glycomed)
WO 92/04735	(Syntex)
WO 95/19965	(Glycomed)
WO 95/22966	(Sanofi Winthrop)
WO 95/33709	(Roche)
WO 96/23791	(Syntex)
WO 96/16027	(Syntex/Agouron)
WO 97/03783	(British Biotech)
WO 97/18207	(DuPont Merck)
WO 98/38179	(GlaxoWellcome)
WO 98/47863	(Labs Jaques Logeais)

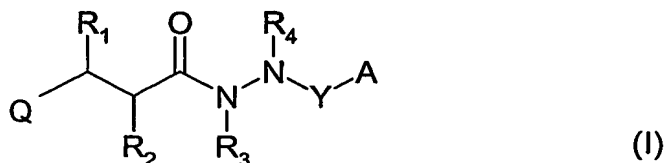
The pharmaceutical utility ascribed to the N-formyl hydroxylamine derivatives in those publications is the ability to inhibit matrix metalloproteinases (MMPs) and in some cases release of tumour necrosis factor (TNF), and hence the treatment of diseases or conditions mediated by those enzymes, such as cancer and rheumatoid arthritis.

In addition to these, US-A-4,738,803 (Roques et al.) also discloses N-formyl hydroxylamine derivatives. However, these compounds are disclosed as enkephalinase inhibitors and are proposed for use as antidepressants and hypotensive agents. Also, WO 97/38705 (Bristol-Myers Squibb) discloses certain N-formyl hydroxylamine derivatives as enkephalinase and angiotensin converting enzyme inhibitors.

There are too many publications relating to metalloenzyme inhibiting hydroxylamic acid derivatives to summarise effectively. However a recent review, Whittaker et. al. Chem. Rev. 1999, 99, 2735, provides an overview of that art.

Description of the invention

The present invention provides a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof



wherein

Q represents a radical of formula -N(OH)CH(=O) or formula -C(=O)NH(OH);

Y represents -C(=O)-, -C(=S)-, -S(=O)-, or -SO₂-;

R₁ represents hydrogen, C₁-C₆ alkyl or C₁-C₆ alkyl substituted by one or more halogen atoms, or, except when Q is a radical of formula -N(OH)CH(=O), a hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkenyloxy, halogen, amino, C₁-C₆ alkylamino, or di-(C₁-C₆ alkyl)amino group;

R₂ represents a substituted or unsubstituted C₁-C₆ alkyl, C₁-C₃ alkyl-O-C₁-C₃ alkyl,

C₁-C₃ alkyl-S-C₁-C₃ alkyl, cycloalkyl(C₁-C₃ alkyl)-, aryl(C₁-C₃ alkyl)-, heterocyclyl(C₁-C₃ alkyl)-, or R¹R²N-C₁-C₃ alkyl group wherein R¹ represents hydrogen or C₁-C₃ alkyl and R² represents C₁-C₃ alkyl, or R¹R²N- represents a cyclic amino group;

R₃ and R₄ taken together with the nitrogen atoms to which they are respectively attached form a saturated heterocyclic ring of from 4 to 7 ring atoms, which may be fused to a second carbocyclic or heterocyclic ring, either of which rings may optionally be substituted; and

A represents a primary, secondary or tertiary amino group or a group -R₅, -OR₅, wherein R₅ is a substituted or unsubstituted C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, cycloalkyl, aryl, heterocyclyl, C₁-C₃ alkyl-O-C₁-C₃ alkyl, C₁-C₃ alkyl-S-C₁-C₃ alkyl, cycloalkyl(C₁-C₃ alkyl)-, heterocyclic(C₁-C₃ alkyl, aryl(C₁-C₃ alkyl)-, or R¹R²N-C₁-C₃ alkyl group wherein R¹ represents hydrogen or C₁-C₃ alkyl and R² represents C₁-C₃ alkyl, or R¹R²N- represents a cyclic amino group.

In another aspect, the invention provides a method for the treatment of bacterial infections in humans and non-human mammals, which comprises administering to a subject suffering such infection an antibacterially effective dose of a compound of formula (I) as defined above. Also included in the invention is the use of a compound of formula (I) as defined above for inhibiting bacterial growth in vitro and in vivo in mammals, and the use of such a compound for the manufacture of a composition for treating bacterial infection by inhibiting bacterial growth.

In a further aspect of the invention there is provided a method for the treatment of bacterial contamination by applying an antibacterially effective amount of a compound of formula (I) as defined above to the site of contamination.

The compounds of formula (I) as defined above may be used as component(s) of antibacterial cleaning or disinfecting materials.

As used herein terms of the form "(C_a-C_b)alkyl" where a and b are integers refer to a

straight or branched chain alkyl moiety having from a to b carbon atoms. Thus, for example, the term "(C₁-C₆)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein terms of the form "divalent (C_a-C_b)alkylene radical" where a and b are integers refer to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valencies.

As used herein terms of the form "(C_a-C_b)alkenyl" where a and b are integers refer to straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. Thus, for example, the term "(C₁-C₆)alkenyl" means a straight or chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond, and includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_a-C_b alkynyl" where a and b are integers refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. Thus, for example, the term "(C₁-C₆)alkynyl" would include for example, ethynyl, 1-propynyl, 1- and 2-butyne, 2-methyl-2-propynyl, 2-pentyne, 3-pentyne, 4-pentyne, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic group, and to groups consisting of two covalently linked monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and naphthyl.

As used herein the term "heteroaryl" refers to a 5- or 6- membered aromatic ring

containing one or more heteroatoms. Illustrative of such groups are thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a 5-7 membered aromatic or non-aromatic heterocyclic ring containing one or more heteroatoms selected from S, N and O, including for example, pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzofuranyl, pyranlyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be, for example, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy, hydroxy(C₁-C₆)alkyl, mercapto, mercapto(C₁-C₆)alkyl, (C₁-C₆)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, -COOH, -COOR^A, -COR^A, -SO₂R^A, -CONH₂, -SO₂NH₂, -CONHR^A, -SO₂NHR^A, -CONR^AR^B, -SO₂NR^AR^B, -NH₂, -NHR^A, -NR^AR^B, -OCONH₂, -OCONHR^A, -OCONR^AR^B, -NHCOR^A, -NHCOOR^A, -NR^BCOOR^A, -NH₂SO₂OR^A, -NR^BSO₂OR^A, -NHCONH₂, -NR^ACONH₂, -NHCONHR^B, -NR^ACONHR^B, -NHCONR^AR^B, or -NR^ACONR^AR^B wherein R^A and R^B are independently a (C₁-C₆)alkyl group.

Salts of the compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

There are several actual or potential chiral centres in the compounds according to

the invention because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof. Currently, the preferred stereoconfiguration of the carbon atom carrying the R_2 group is R.

In the compounds of the invention, in relation to the groups Q, R_1 , R_2 , R_3 , R_4 , Y and A, separately and in combination:

The group Q

It is currently preferred that Q is an N-formyl hydroxylamine group $-N(OH)CH(=O)$.

The radical -Y-

It is currently preferred that -Y- is $-C(=O)-$ or $-SO_2-$.

The group R_1

R_1 may be, for example, hydrogen, methyl, trifluoromethyl or, in the case where Q is a hydroxamic acid group $HONHCO-$, fluorine. Hydrogen is currently preferred.

The group R_2

R_2 may be, for example:

optionally substituted C_1 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl or cycloalkyl;

phenyl(C_1 - C_6 alkyl)-, phenyl(C_3 - C_6 alkenyl)- or phenyl(C_3 - C_6 alkynyl)-
optionally substituted in the phenyl ring;

cycloalkyl(C_1 - C_6 alkyl)-, cycloalkyl(C_3 - C_6 alkenyl)- or cycloalkyl(C_3 - C_6 alkynyl)-
optionally substituted in the cycloalkyl ring; or

$CH_3(CH_2)_pO(CH_2)_q-$ or $CH_3(CH_2)_pS(CH_2)_q-$, wherein p is 0, 1, 2 or 3 and q is 1, 2 or 3.

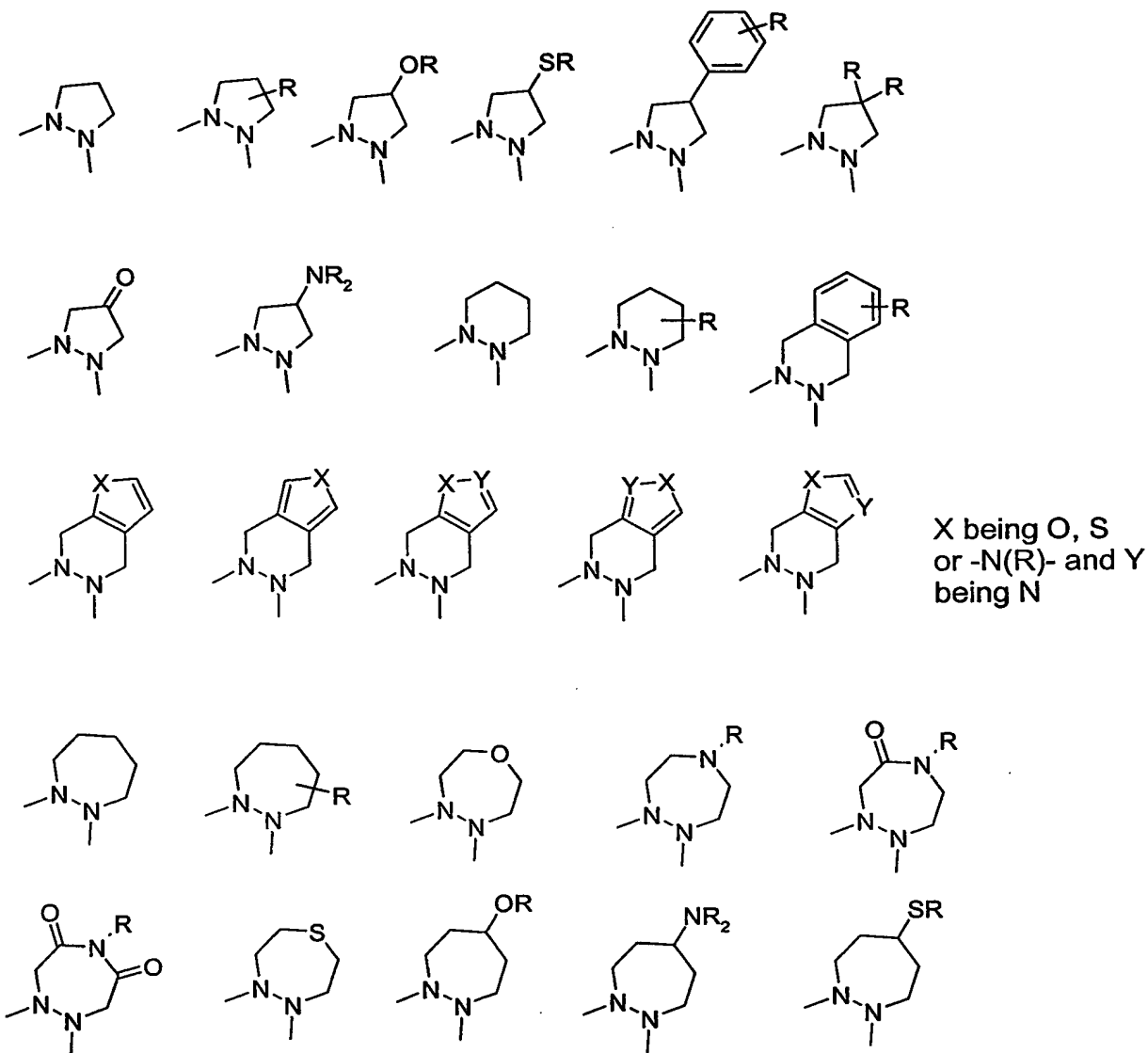
Specific examples of R_2 groups include

methyl, ethyl, n- and iso-propyl, n- and iso-butyl, n-pentyl, iso-pentyl, 3-methyl-but-1-yl, n-hexyl, n-heptyl, n-octyl, methylsulfanylethyl, ethylsulfanylmethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-ethoxymethyl, 3-hydroxypropyl, allyl, 3-phenylprop-3-en-1-yl, prop-2-yn-1-yl, 3-phenylprop-2-yn-1-yl, 3-(2-chlorophenyl)prop-2-yn-1-yl, but-2-yn-1-yl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, furan-2-ylmethyl, furan-3-methyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylmethyl, piperidinylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, phenylpropyl, 4-chlorophenylpropyl, 4-methylphenylpropyl, 4-methoxyphenylpropyl, benzyl, 4-chlorobenzyl, 4-methylbenzyl, and 4-methoxybenzyl.

Presently preferred groups at R_2 are (C_1-C_6) alkyl-, cycloalkylmethyl-, (C_1-C_3) alkyl-S- (C_1-C_3) alkyl-, or (C_1-C_3) alkyl-O- (C_1-C_3) alkyl-, especially n-propyl, n-butyl, n-pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

The ring formed by R_3 and R_4 and the nitrogens to which they are attached

Examples of such rings are the following, wherein R represents hydrogen or C_1-C_4 alkyl



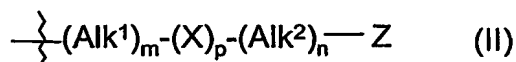
In the above rings, where a sulfur atom is present as a ring member, the equivalent structures wherein that sulfur is oxidised to -SO- or -SO₂- are also examples of ring structures which may be formed by R₃ and R₄ and the nitrogens to which they are attached.

The group A

The group A is a primary, secondary or tertiary amino group or a group -R₅, or -OR₅. When A is -R₅, or -OR₅, the R₅ group may be, for example, any of those given as R₂ examples above, or a group of formula (II) as defined below, including such specific

examples of groups (II) as morpholinyl, furanyl, thienyl, phenyl, and benzyl..

Presently it is preferred that A is a secondary or tertiary amino group, and in the latter case it may be a non-cyclic or a cyclic amino group. For example, A may be an amino group of formula -NR₆R₇ wherein R₆ and R₇ independently represent a radical of formula (II)



wherein

m, p and n are independently 0 or 1;

Z represents hydrogen or a carbocyclic or heterocyclic ring of 5 to 7 ring atoms which is optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms;

Alk¹ and Alk² independently represent divalent C₁-C₃ alkylene radicals;

X represents -O-, -S-, -S(O)-, -S(O₂)-, -C(=O)-, -NH-, -NR₇- where R₇ is C₁-C₃ alkyl;

and wherein

Alk¹, Alk² and Z when other than hydrogen, independently are optionally substituted by

(C₁-C₃)alkyl, (C₂-C₃)alkenyl, or (C₂-C₃)alkynyl,
phenyl, optionally substituted by (C₁-C₃)alkyl, (C₁-C₃)alkoxy, halo, nitro,
amino, mono- or di-(C₁-C₃)alkylamino, cyano or trifluoromethyl;

monocyclic 5 or 6-membered heterocyclic, optionally substituted by (C₁-C₃)alkyl, (C₁-C₃)alkoxy, halo, nitro, amino, mono- or di-(C₁-C₃)alkylamino, cyano or trifluoromethyl

benzyl, optionally substituted in the phenyl ring by (C₁-C₃)alkyl, (C₁-C₃)alkoxy,

halo, nitro, amino, mono- or di-(C₁-C₃)alkylamino, cyano or trifluoromethyl,
 hydroxy, phenoxy, (C₁-C₆)alkoxy, or hydroxy(C₁-C₆)alkyl,
 mercapto, (C₁-C₆)alkylthio or mercapto(C₁-C₆)alkyl,
 oxo,
 nitro,
 cyano
 halo
 -COOH, or -COOR^A,
 -CONH₂, -CONHR^A, or -CONR^AR^B
 -COR^A, -SO₂R^A,
 -NHCOR^A,
 -NH₂, -NHR^A, or -NR^AR^B,

wherein R^A and R^B are independently a (C₁-C₆) alkyl group, R^A and R^B taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring which may be substituted by (C₁-C₃)alkyl, hydroxy, or hydroxy(C₁-C₃)alkyl.

The amino group A may also be one of formula -NR₆R₇ wherein R₆ and R₇ when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring of 5 to 8 atoms optionally fused to a saturated or unsaturated carbocyclic or heterocyclic second ring of 5 to 7 ring atoms, any of which rings being optionally substituted by a radical of formula (II) as defined above. Examples of cyclic amino groups are 1-pyrrolidinyl, piperidin-1-yl, 1-piperazinyl, hexahydro-1-pyridazinyl, morpholin-4-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide, hexahydroazipino, thiomorpholino, diazepino, and thiazolidinyl. Presently preferred are piperidin-1-yl and 1-piperazinyl.

The group of formula (II)

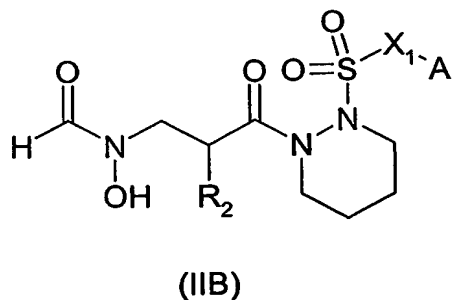
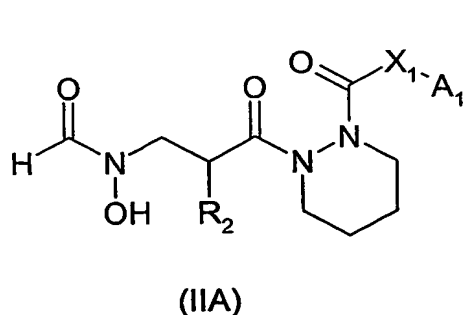
In the substituent (II) Alk¹ and Alk² may independently represent, for example

$-(CH_2)-$ or $-(CH_2CH_2)-$. In the case where m is 0 and p is 1, X may be, for example $-S-$, $-S(=O)-$, or preferably $-C(=O)-$ or $-S(O_2)-$. In such cases n may be 0 or 1, and when A is a cyclic amino group which contains a second ring nitrogen, the X radical may be linked to that ring nitrogen, for example (in the case of $X = -C(=O)-$ or $-S(O_2)-$) as an amide or sulphonamide bond.

In the substituent (II) m , n and p may all be 0, so that the group Z is directly linked to the amino group A .

In a preferred subset of the compounds of the invention, the substituent (II) has the formula $-CH_2Z$, $-OZ$, or $-(C=O)Z$ wherein Z is C_1 - C_3 alkyl, phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidinyl, 1,2,3-thiadiazolyl, 1,4-thiazolyl, benzofuranyl, furanyl, thienyl, pyranal, pyrrolyl, pyrazolyl, isoxazolyl, or pyridyl, any of which may optionally be substituted as specified. In particular, Z may be a methyl, ethyl, n - or iso-propyl, phenyl, 3,4-methylenedioxyphenyl, morpholinyl, pyrimidin-2-yl, 1,2,3-thiadiazol-5-yl, 1,4-thiazol-5-yl, benzofuran-2-yl, 2- or 3-furanyl, 2- or 3-thienyl, 2- or 3-pyranal, 2-, 3- or 4-pyrrolyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, or 2-, 3- or 4-pyridyl ring any of which may optionally be substituted as specified in the broad description of the compounds of the invention.

Compounds of the invention include those selected from the group consisting of compounds of formulae (IIA) or (IIB).



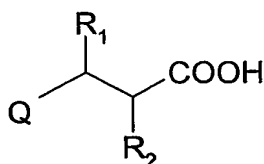
wherein R_2 is as defined in relation to formula (II), especially n -propyl, n -butyl, n -pentyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl;

X₁ is a bond, C₁-C₃ alkylene, -NH- or -O-; and

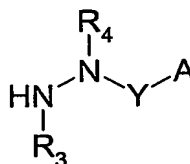
A₁ is optionally substituted C₁-C₆ alkyl, cycloalkyl, aryl, or heterocyclic, for example methyl, ethyl phenyl, cyclopentyl, cyclohexyl, 2- or 3-furanyl, 2- or 3- thienyl, 2-, 3- or 4-pyridyl, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-oxazolyl, or 3-, 4- or 5-thiazolyl, methoxymethyl, 3,5-bis-(trifluoromethyl)phenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 3,4-methylenedioxyphenyl, 4-fluorophenyl benzyl, 3-pyridyl, 4-pyridyl, cyclohexyl, 1,3-dimethylpyrazol-5-yl, 1-methylimidazol-5-yl, and 2-[morpholin-1-yl]pyrid-5-yl.

Particular compounds of the invention include those of the Examples herein.

In general, compounds of the invention are accessible by conventional synthetic procedures, for example by acylation of cyclic diazole compound (IV) with an activated derivative of an acid (III),

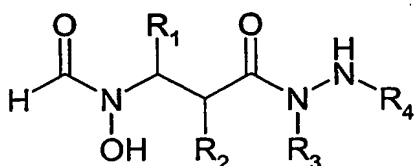


(III)

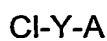


(IV)

by methods known from peptide synthesis for example using an acid chloride, wherein the NH and/or OH groups in Q are protected during the acylation and deprotected thereafter. Other compounds of the invention may be prepared by reaction of a compound of formula (V) with a chloride of formula (VI) or an isocyanate of formula (VII):



(V)



(VI)



(VII)

The Examples herein provide further details of routes and methods for the preparation of compounds of the invention.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood

that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples illustrate embodiments of the invention.:

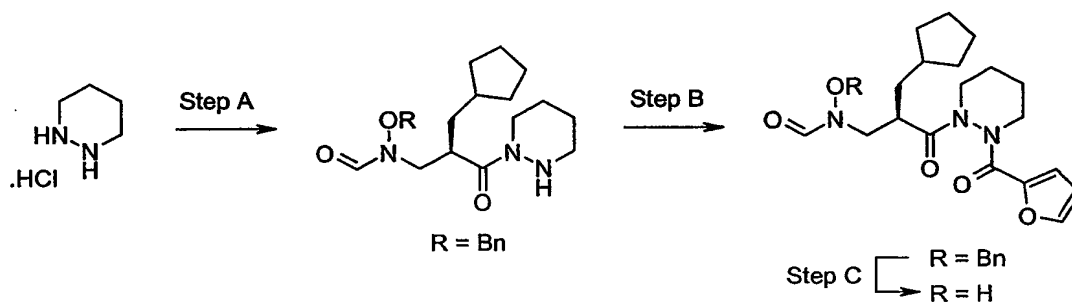
In the Examples, the following abbreviations have been used:

DMF	Dimethylformamide
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LRMS	Low resolution mass spectrometry
NMR	Nuclear magnetic resonance
RT	Retention Time
TLC	Thin layer chromatography
DIEA	N,N-diisopropylethylamine
DCM	Dichloromethane
HATU	O-(7-Azabenzotriazo-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

^1H and ^{13}C NMR spectra were recorded using a Bruker DPX 250 spectrometer at 250.1 and 62.9MHz, respectively. Mass spectra were obtained using a Perkin Elmer Sciex API 165 spectrometer using both positive and negative ionisation modes. Infra-red spectra were recorded on a Perkin Elmer PE 1600 FTIR spectrometer. Analytical HPLC was performed on a Beckman System Gold, using Waters Nova Pak C18 column (150 mm, 3.9 mm) with 20 to 90 % solvent B gradient (1 ml/min) as the mobile phase. [Solvent A: 0.05% TFA in 10% water 90% methanol; Solvent B: 0.05% TFA in 10% methanol 90%], detection wavelength at 230 nm. Preparative HPLC was performed on a Gilson autoprep instrument using a C18 Waters delta prep-pak cartridge (15 μm , 300 A, 25 mm, 10 mm) with 20 to 90 % solvent B gradient

(6 ml/min) as the mobile phase. [Solvent A water; Solvent B: methanol], UV detection was at 230 nm.

Example 1



Step A. 3-Benzyloxyformylamino-(2*R*)-cyclopentylmethyl-propionic acid, EDAC, HOBT, DMF, 0°C to rt, 5 h; Step B. 2-furoyl chloride, DIEA, CH₂Cl₂, 0°C to rt, 16 h; Step C. H₂ (g), 10% Pd/C, MeOH, rt, 2 h.

Step A:

N-Benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-(tetrahydropyridazin-1-yl)propyl]formamide

To a solution of 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl-propionic acid (3.73 g, 12.2 mmol) in DMF (40 ml) at 0°C under argon was added EDAC (2.58 g, 13.5 mmol) and HOBT (0.83 g, 6.12 mmol). The resulting mixture was stirred for 15 min at 0°C before 1,2-diazacyclohexane hydrochloride (1.50 g, 12.2 mmol) was introduced followed by DIEA (4.69 ml, 27.0 mmol) in DMF (5 ml). The reaction was maintained at 0°C for 1 h and then warmed to rt where it was left for 5 h. After this time, the reaction was diluted with EtOAc and washed with 1M Na₂CO₃. The aqueous phase was removed and extracted with additional EtOAc (x1). The combined organic fractions were washed with H₂O and sat. NaCl and then separated, dried (MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by chromatography on silica eluting with 100% EtOAc. This gave the title compound as a colourless oil (2.95 g, 65%). ¹H-NMR; δ (CD₃OD), 8.18 (0.5H, s, CHO), 7.88

(0.5H, s, CHO), 7.50-7.30 (5H, m, ArH), 4.92-4.65 (2H, br m, CH₂Ph), 4.10-2.80 (7H, m), 1.75-1.40 (13H, m), 1.20-1.00 (2H, m). LRMS: +ve ion: 396 [M+23], 374 [M+1], 346.

Step B:

N-Benzyloxy-*N*-{(2*R*)-cyclopentylmethyl-3-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl}formamide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-(tetrahydropyridazin-1-yl)propyl]formamide (60 mg, 0.16 mmol) in DCM (1 ml) at 0°C under argon was added 2-furoyl chloride (17 µl, 0.17 mmol) followed by DIEA (34 µl, 0.19 mmol). The mixture was stirred for 30 min at 0°C and then warmed to rt where it was maintained for 16 h. After this time the reaction was diluted with EtOAc and washed with 1M citric acid, sat. NaHCO₃ and sat. NaCl. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by chromatography on silica eluting with 70-100% EtOAc/hexanes. This gave the title compound as a colourless oil (67 mg, 89%). ¹H-NMR; δ (CD₃OD), 8.26 (0.33H, s, CHO), 7.95 (0.67H, s, CHO), 7.78 (1H, br s, HetArH), 7.50-7.25 (5H, m, ArH), 7.03 (1H, br m, HetArH), 6.63-6.52 (1H, br m, HetArH), 5.03-4.70 (2H, br m, CH₂Ph), 4.70-4.40 (2H, m), 4.30-2.85 (5H, m), 1.90-1.00 (13H, m), 0.95-0.60 (2H, m). LRMS: +ve ion: 490 [M+23].

Step C:

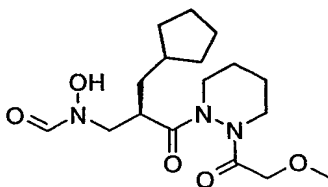
(2*R*)-Cyclopentylmethyl-3-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl}formamide

To a solution of the *N*-benzyloxy-*N*-{(2*R*)-cyclopentylmethyl-3-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl}formamide (65 mg, 0.14 mmol) in MeOH (3 ml) at rt under argon was added 10% Pd/C (8 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 2 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (52 mg, 100%). ¹H-NMR; δ (CD₃OD), 8.29 (0.33H, s, CHO), 7.89

(0.67H, s, CHO), 7.78 (1H, br s, HetArH), 7.20-7.00 (1H, br m, HetArH), 6.64 (1H, br m, HetArH), 4.70-4.55 (2H, m), 3.95-2.95 (5H, m), 1.95-1.0 (13H, m), 0.95-0.80 (2H, m). LRMS: +ve ion: 400 [M+23]. HPLC Rt = 4.49 min (214 nm).

The compounds of the following Examples 2 – 12 were prepared by method of Example 1:

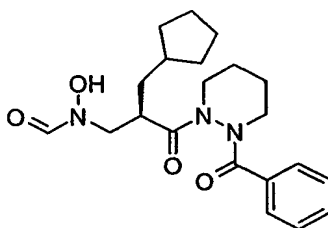
Example 2



N-((2*R*)-Cyclopentylmethyl-3-[2-(2-methoxyacetyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 378 [M+23]. HPLC Rt = 4.61 and 4.64 min [rotamers] (214 nm).

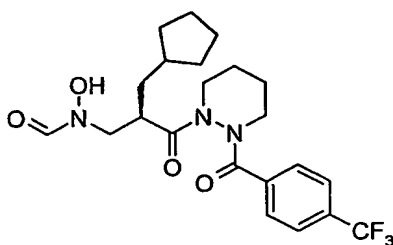
Example 3



N-((2*R*)-Cyclopentylmethyl-3-[2-benzoyl-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 410 [M+23], 191. HPLC Rt = 5.24 min (214 nm).

Example 4

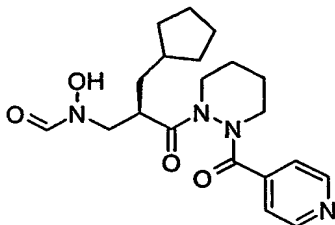


21

N-((2*R*)-Cyclopentylmethyl-3-[2-(4-trifluoromethylbenzoyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 478 [M+23], 259. HPLC Rt = 5.47 min (214 nm).

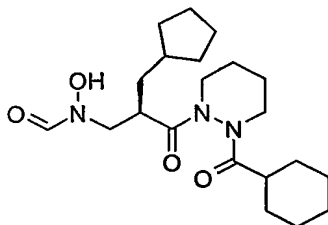
Example 5



N-((2*R*)-Cyclopentylmethyl-3-[2-(pyridine-4-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 411 [M+23], 389 [M+1], 192. HPLC Rt = 1.00 min (214 nm).

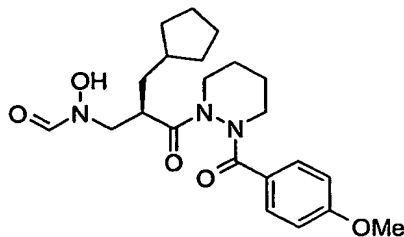
Example 6



N-((2*R*)-Cyclopentylmethyl-3-[2-cyclohexanecarbonyl-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 416 [M+23], 197. HPLC Rt = 5.29 min (214 nm).

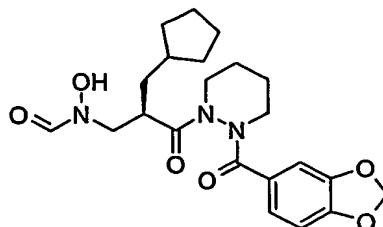
Example 7



N-((2*R*)-Cyclopentylmethyl-3-[2-(4-methoxybenzoyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 440 [M+23], 221. HPLC Rt = 4.91 min (214 nm).

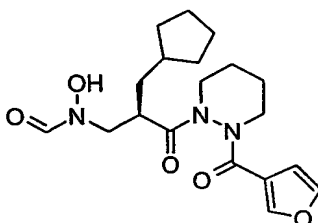
Example 8



N-((2*R*)-Cyclopentylmethyl-3-[2-(benzo[1,3]dioxole-5-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 454 [M+23], 235. HPLC Rt = 4.84 min (214 nm).

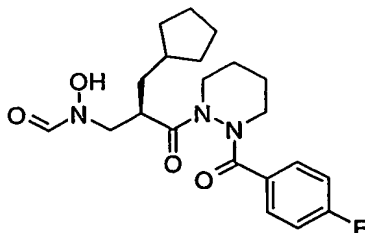
Example 9



N-((2*R*)-Cyclopentylmethyl-3-[2-(furan-3-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 400 [M+23], 181.

Example 10

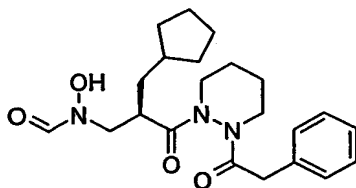


N-((2*R*)-Cyclopentylmethyl-3-[2-(4-fluorobenzoyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 428 [M+23], 209. HPLC Rt = 5.01 min (214 nm).

23

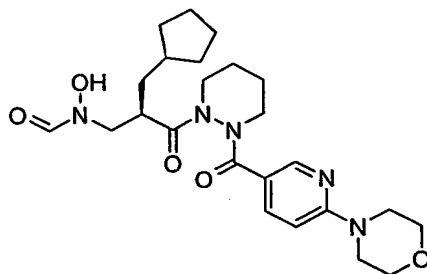
Example 11



N-((2R)-Cyclopentylmethyl-3-[2-phenylacetyl-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 424 [M+23], 205. HPLC Rt = 5.15 and 5.25 min [rotamers] (214 nm).

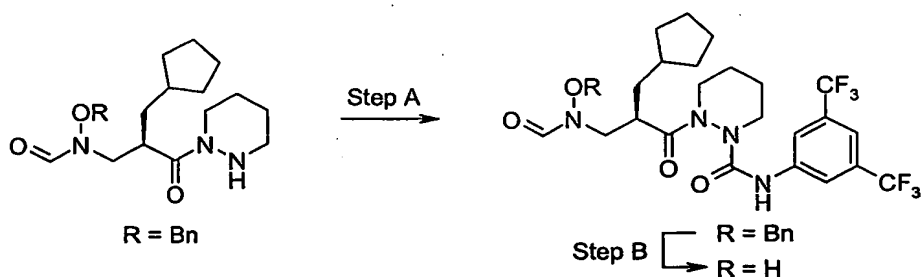
Example 12



N-((2R)-Cyclopentylmethyl-3-[2-(6-morpholin-4-yl-pyridine-3-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 496 [M+23], 474 [M+1], 277, 191. HPLC Rt = 1.84 min (214 nm).

Example 13



Step A. 3,5-Bis-(trifluoromethyl)phenyl isocyanate, EtOAc, rt, 16 h; Step B. H₂ (g), 10% Pd/C, MeOH, rt, 2 h.

Step A:

2-[3-(Benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-tetrahydropyridazine-1-carboxylic acid (3,5-bis-(trifluoromethyl)phenyl)amide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-(tetrahydropyridazin-1-yl)propyl]formamide (53 mg, 0.14 mmol) in EtOAc (2 ml) at rt under argon was added 3,5-bis-(trifluoromethyl)phenyl isocyanate (36 mg, 0.14 mmol). The resulting mixture was stirred for 16 h at rt and then concentrated under reduced pressure. The crude product was purified by chromatography on silica eluting with 70-100% EtOAc/hexanes to give the title compound as a colourless oil (76 mg, 85%). ¹H-NMR; δ(CD₃OD), 8.25-7.88 (3H, m, ArH and CHO), 8.60-7.20 (6H, m, ArH), 5.01-4.75 (2H, m, CH₂Ph), 4.60-2.90 (7H, m), 1.80-1.05 (13H, m), 1.00-0.90 (2H, m). LRMS: +ve ion: 651 [M+23], 400.

Step B:

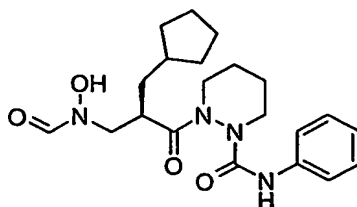
2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (3,5-bis-(trifluoromethyl)phenyl)amide

To a solution of the 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-tetrahydropyridazine-1-carboxylic acid (3,5-bis-(trifluoromethyl) phenyl)amide (75 mg, 0.12 mmol) in MeOH (4 ml) at rt under argon was added 10% Pd/C (10 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 2 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (63 mg, 98%). ¹H-NMR; δ(CD₃OD), 8.30-8.24 (2.5H, m, ArH and CHO), 7.91 (0.5H, s, CHO), 7.62 (1H, s, ArH), 4.60-4.38 (2H, m), 4.10-2.85 (5H, m), 1.90-1.05 (13H, m), 1.00-0.90 (2H, m). LRMS: +ve ion: 561 [M+23]. HPLC Rt = 6.30 min (214 nm).

The compounds of Examples 14 to 20 were prepared by methods analogous to that of Example 2 substituting the appropriate isocyanate for that used in Example 13

Example 14

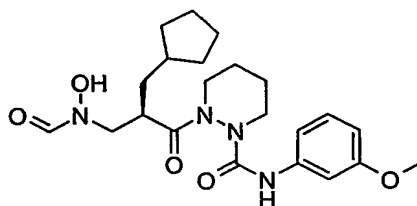
25



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid phenylamide

LRMS: +ve ion: 425 [M+23]. HPLC Rt = 5.13 min (214 nm).

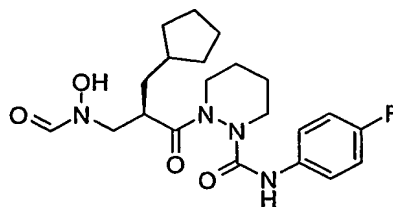
Example 15



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (3-methoxyphenyl)amide

LRMS: +ve ion: 455 [M+23]. HPLC Rt = 5.13 min (214 nm).

Example 16

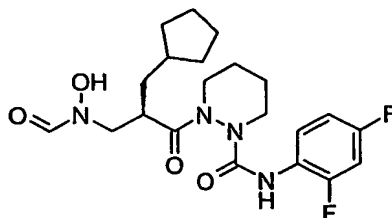


2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (4-fluorophenyl)amide

LRMS: +ve ion: 443 [M+23]. HPLC Rt = 5.22 min (214 nm).

Example 17

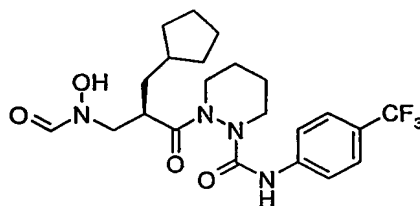
26



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (2,4-bis(fluoro)phenyl)amide

LRMS: +ve ion: 461 [M+23]. HPLC Rt = 5.15 min (214 nm).

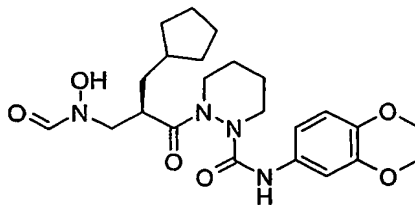
Example 18



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (4-trifluoromethylphenyl)amide

LRMS: +ve ion: 493 [M+23]. HPLC Rt = 5.81 min (214 nm).

Example 19

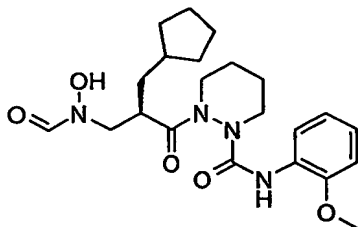


2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (2,3,4a,8a-tetrahydrobenzo[1,4]dioxin-6-yl)amide

LRMS: +ve ion: 483 [M+23]. HPLC Rt = 4.96 min (214 nm).

Example 20

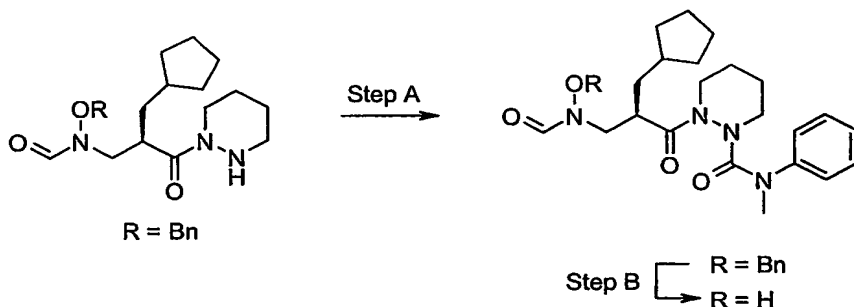
27



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid (2-methoxyphenyl)amide

LRMS: +ve ion: 455 [M+23]. HPLC Rt = 5.27 and 5.37 min [rotamers] (214 nm).

Example 21



Step A. N-Methyl-N-phenyl carbamoyl chloride, THF, DIEA, microwave irradiation (100W), 140°C, 12 min; Step B. H₂ (g), 10% Pd/C, MeOH, rt, 1 h.

Step A:

2-[3-(Benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-tetrahydropyridazine-1-carboxylic acid methylphenylamide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-(tetrahydropyridazin-1-yl)propyl]formamide (65 mg, 0.174 mmol) in THF containing DIEA (33 μ l, 0.19 mmol) at rt in air was added *N*-methyl-*N*-phenyl carbamoyl chloride (30 mg, 0.174 mmol). The mixture was then irradiated with microwaves (100W) at 140°C for 12 min. After this time the reaction was concentrated under reduced pressure and the crude product was purified by preparative HPLC to give the product as a colourless solid (8 mg, 7%). LRMS: +ve ion: 529 [M+23], 396.

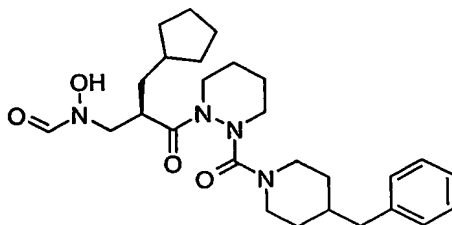
Step B:

2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid methylphenylamide

To a solution of 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-tetrahydropyridazine-1-carboxylic acid methylphenylamide (6 mg, 0.08 mmol) in MeOH (1 ml) at rt under argon was added 10% Pd/C (1 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (2 mg, 41%). LRMS: +ve ion: 439 [M+23], 239. HPLC Rt = 5.62 min (214 nm).

The compound of Example 22 was prepared by the method of Example 21 of Example 10 substituting the appropriate carbamoyl chloride for that used in Example 21

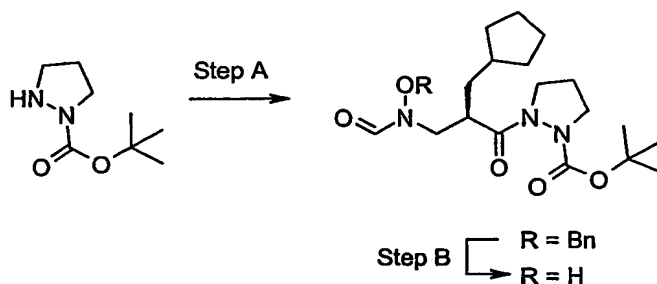
Example 22



N-[(2*R*)-Cyclopentylmethyl-3-[2-(4-benzylpiperidine-1-carbonyl)-tetrahydropyridazin-1-yl]-3-oxo-propyl]-N-hydroxyformamide

LRMS: +ve ion: 507 [M+23], 485 [M+1], 310, 249, 176. HPLC Rt = 5.90 and 6.32 min [rotamers] (214 nm).

Example 23



Step A. 3-Benzyloxyformylamino-(2*R*)-cyclopentylmethyl-propionic acid, HATU, DIEA, DMF, 0°C to rt, 2.5 h; Step B. H₂ (g), 10% Pd/C, MeOH, rt, 2 h.

Step A:

2-[3-(Benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-carboxylic acid *tert*-butyl ester

To a solution of 3-benzyloxyformylamino-(2*R*)-cyclopentylmethyl-propionic acid (103 mg, 0.34 mmol) in DMF (2 ml) at 0°C under argon was added HATU (128 mg, 0.34 mmol) and DIEA (70 μ l, 0.41 mmol). The resulting mixture was stirred for 10 min before a solution of *N*-*tert*-(butoxycarbonyl)-1,2-diazacyclopentane (58 mg, 0.34 mmol) in DMF (0.5 ml) was introduced. After 1 h at 0°C, the reaction was warmed to rt where it was maintained for 1.5 h. The mixture was then diluted with EtOAc and washed with 1M citric acid, 1M Na₂CO₃ and sat. NaCl. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica eluting with 50-70% EtOAc/hexanes to give the title compound as a colourless oil (46 mg, 30%). ¹H-NMR; δ (CDCl₃), 8.23 (0.25H, s, CHO), 8.08 (0.25H, s, CHO), 7.99 (0.25 H, s, CHO), 7.85 (0.25H, s, CHO), 7.45-7.26 (5H, m, ArH), 4.87-4.60 (2H, br m, CH₂Ph), 4.20-2.80 (7H, m), 2.10-1.40 (11H, m), 1.45 (9H, s, (CH₃)₃), 1.20-1.00 (2H, m). LRMS: +ve ion: 482 [M+23], 382.

Step B:

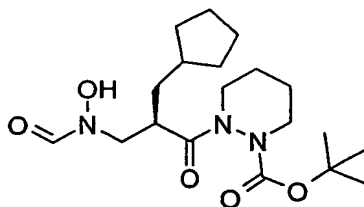
2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid *tert*-butyl ester

To a solution of 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-

pyrazolidine-1-carboxylic acid *tert*-butyl ester (46 mg, 0.10 mmol) in MeOH (4 ml) at rt under argon was added 10% Pd/C (8 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 2 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (36 mg, 97%). ¹H-NMR; δ (CD₃OD), 8.28 (0.25H, s, CHO), 8.22 (0.25H, s, CHO), 7.93 (0.25H, s, CHO), 7.80 (0.25H, s, CHO), 4.20-3.79 (4H, m), 3.78-3.40 (1H, m), 3.39-3.02 (2H, m), 2.20-1.40 (11H, m), 1.51 (4.5H, s, (CH₃)₃), 1.50 (4.5H, s, (CH₃)₃), 1.20-1.01 (2H, m). LRMS: +ve ion: 392 [M+23], 292, 270. HPLC Rt = 5.23 min (214 nm).

The compound of Example 24 was prepared by a method analogous to that to Example 23:

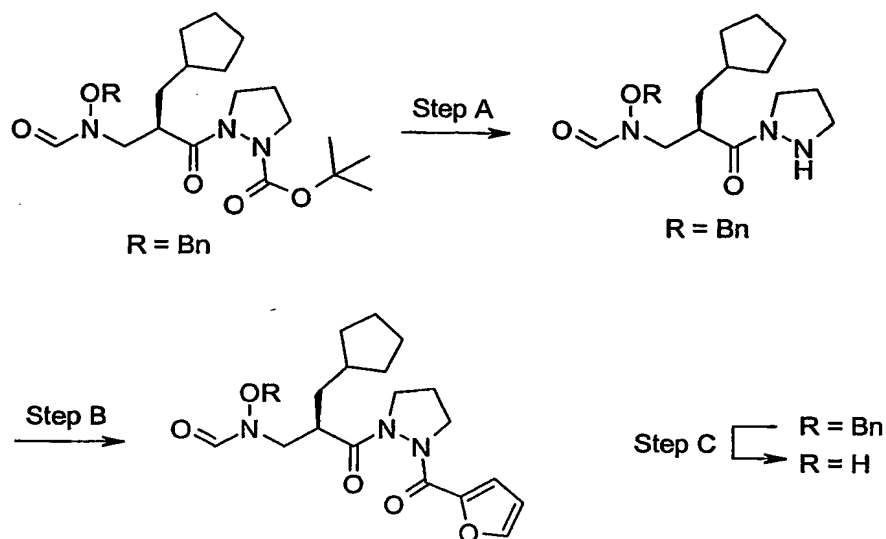
Example 24



2-[(2*R*)-Cyclopentylmethyl]-3-(formylhydroxyamino)-propionyl]-tetrahydropyridazine-1-carboxylic acid *tert*-butyl ester

¹H-NMR; δ (CD₃OD), 8.26 (0.25H, s, CHO), 7.91 (0.25H, s, CHO), 7.84 (0.5H, s, CHO), 4.44-4.40 (1H, m), 4.22-3.10 (4H, m), 3.10-2.70 (2H, m), 1.85-1.30 (13H, m), 1.51 (4.5H, s, (CH₃)₃), 1.50 (4.5H, s, (CH₃)₃), 1.20-1.00 (2H, m). LRMS: +ve ion: 406 [M+23], 306. HPLC Rt = 5.41 and 5.55 min [rotamers] (214 nm).

Example 25



Step A. $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 :AcOH (5:1), 0°C 2 h; Step B. 2-furoyl chloride, DIEA, CH_2Cl_2 , 0°C to rt, 1 h; Step C. H_2 (g), 10% Pd/C, MeOH, rt, 1 h.

Step A:

N-Benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-pyrazolidin-1-yl-propyl]formamide

To a solution of 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-carboxylic acid *tert*-butyl ester (477 mg, 1.04 mmol) in DCM (12.5 ml) at 0°C under argon was added glacial acetic acid (2.5 ml) followed by boron trifluoride etherate (0.77 ml, 6.24 mmol). The solution was stirred at 0°C for 2 h and then diluted with EtOAc. The mixture was washed with 1M Na_2CO_3 and sat. NaCl. The organic layer was dried (MgSO_4), filtered and concentrated under reduced pressure to give the title compound which was used without further purification. $^1\text{H-NMR}$; $\delta(\text{CDCl}_3)$, 8.19 (0.5H, s, CHO), 7.88 (0.5H, s, CHO), 7.47-7.26 (5H, m, ArH), 4.95-4.60 (2H, br m, CH_2Ph), 3.93-3.30 (5H, m), 3.20-2.80 (2H, m), 2.00-1.40 (12H, m), 1.15-1.00 (2H, m). LRMS: +ve ion: 382 [$\text{M}+23$], 332.

Step B:

N-Benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-[2-(furan-2-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl]formamide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-pyrazolidin-1-yl-propyl]formamide (31 mg, 0.086 mmol) in DCM (2 ml) at 0°C under argon was added 2-furoyl chloride (9 µl, 0.095 mmol) followed by DIEA (18 µl, 0.104 mmol). The mixture was stirred for 30 min at 0°C and then warmed to rt where it was maintained for 1 h. After this time the reaction was diluted with EtOAc and washed with 1M citric acid, sat. NaHCO₃ and sat. NaCl. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure. The crude material was purified by chromatography on silica eluting with 80% EtOAc/hexanes. This gave the title compound as a colourless oil (34 mg, 87%). ¹H-NMR; δ(CD₃OD), 8.32 (0.25H, s, CHO), 8.10 (0.25H, s, CHO), 7.96 (0.25H, s, CHO), 7.90 (0.25H, s, CHO), 7.80-7.74 (1H, br m, HetArH), 7.50-7.20 (6H, br m, ArH and HetArH), 6.60 (1H, br s, HetArH), 5.00-4.80 (2H, br m, CH₂Ph), 4.40-2.95 (7H, m), 2.20-1.40 (11H, m), 1.20-0.85 (2H, m). LRMS: +ve ion: 476 [M+23].

Step C:

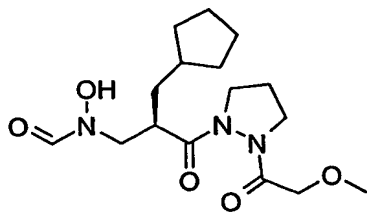
(2*R*)-Cyclopentylmethyl-3-[2-(furan-2-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl}formamide

To a solution of the *N*-benzyloxy-*N*-{(2*R*)-cyclopentylmethyl-3-[2-(furan-2-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl}formamide (32 mg, 0.071 mmol) in MeOH (2 ml) at rt under argon was added 10% Pd/C (5 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (23 mg, 90%). ¹H-NMR; δ(CD₃OD), 8.28 (0.25H, s, CHO), 8.22 (0.25H, s, CHO), 7.90-7.70 (1.5H, m, CHO and HetArH), 7.30-7.20 (1H, br m, HetArH), 6.65 (1H, br s, HetArH), 4.40-3.05 (7H, m), 2.25-1.30 (11H, m), 1.20-0.85 (2H, m). LRMS: +ve ion: 386 [M+23]. HPLC Rt = 4.36 min (214 nm).

The compounds of Examples 26 – 37 were prepared by the method of Example 25:

33

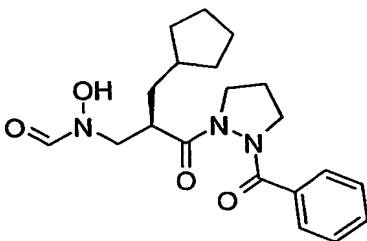
Example 26



N-((2*R*)-Cyclopentylmethyl-3-[2-(2-methoxyacetyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 364 [M+23], 167. HPLC Rt = 2.39 min (214 nm).

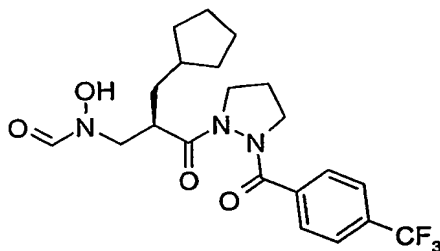
Example 27



N-((2*R*)-Cyclopentylmethyl-3-[2-benzoyl-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 396 [M+23], 177. HPLC Rt = 4.72 min (214 nm).

Example 28

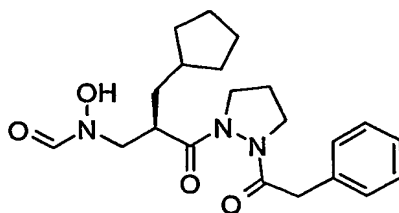


N-((2*R*)-Cyclopentylmethyl-3-[2-(4-trifluoromethylbenzoyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 464 [M+23], 245. HPLC Rt = 5.36 min (214 nm).

34

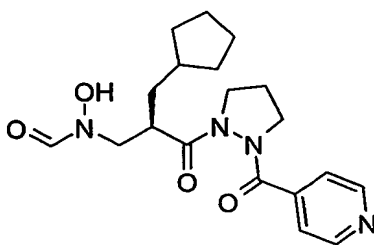
Example 29



N-((2*R*)-Cyclopentylmethyl-3-[2-phenylacetyl-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 410 [M+23], 191. HPLC Rt = 4.97 min (214 nm).

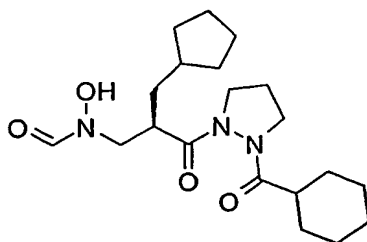
Example 30



N-((2*R*)-Cyclopentylmethyl-3-[2-(pyridine-4-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 397 [M+23], 178. HPLC Rt = 0.99 min (214 nm).

Example 31

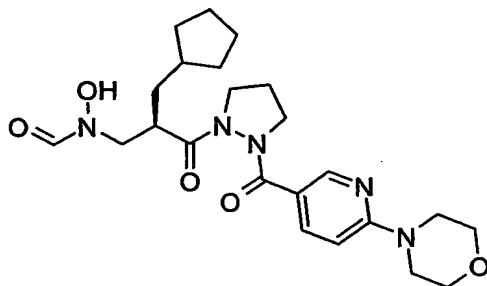


N-((2*R*)-Cyclopentylmethyl-3-[2-cyclohexanecarbonyl-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 402 [M+23], 183. HPLC Rt = 5.16 min (214 nm).

35

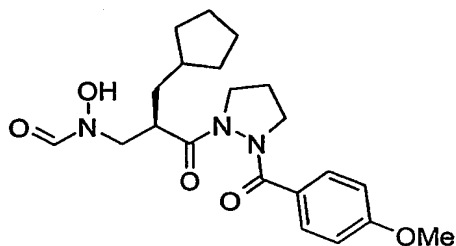
Example 32



N-((2*R*)-Cyclopentylmethyl-3-[2-(6-morpholin-4-yl-pyridine-3-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 459 [M+23], 460 [M+1]. HPLC Rt = 1.43 min (214 nm).

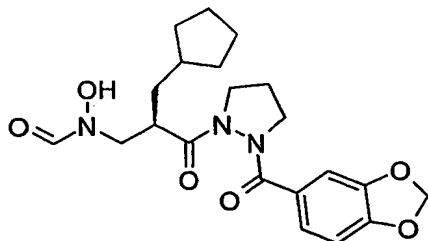
Example 33



N-((2*R*)-Cyclopentylmethyl-3-[2-(4-methoxybenzoyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 426 [M+23], 207. HPLC Rt = 4.88 min (214 nm).

Example 34

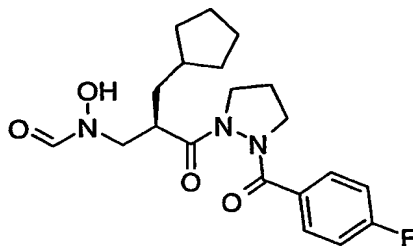


N-((2*R*)-Cyclopentylmethyl-3-[2-(benzo[1,3]-dioxole-5-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 440 [M+23], 221. HPLC Rt = 4.75 min (214 nm).

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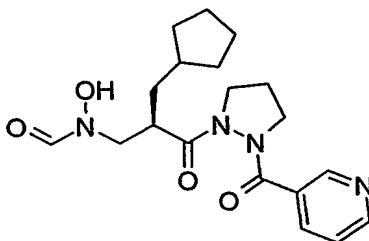
Example 35



N-((2*R*)-Cyclopentylmethyl-3-[2-(4-fluorobenzoyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 414 [M+23], 195. HPLC Rt = 4.90 min (214 nm).

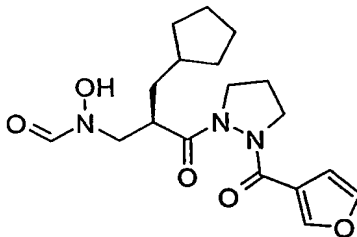
Example 36



N-((2*R*)-Cyclopentylmethyl-3-[2-(pyridine-3-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 397 [M+23], 178. HPLC Rt = 0.99 min (214 nm).

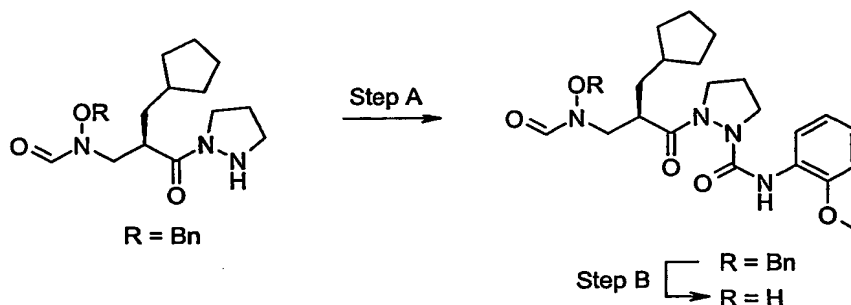
Example 37



N-((2*R*)-Cyclopentylmethyl-3-[2-(furan-3-carbonyl)-pyrazolidin-1-yl]-3-oxo-propyl)-N-hydroxyformamide

LRMS: +ve ion: 386 [M+23], 167. HPLC Rt = 4.47 min (214 nm).

Example 38



Step A. 2-Methoxyphenyl isocyanate, EtOAc, rt, 16 h; Step B. H₂ (g), 10% Pd/C, MeOH, rt, 2 h.

Step A:

2-[3-(Benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-carboxylic acid (2-methoxyphenyl)amide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-propionyl]-pyrazolidine-1-carboxylic acid (2-methoxyphenyl)amide (37 mg, 0.10 mmol) in EtOAc (2 ml) at rt under argon was added 2-methoxyphenyl isocyanate (15 mg, 0.10 mmol). The resulting mixture was stirred for 16 h at rt and then concentrated under reduced pressure. The crude product was purified by preparative HPLC to give the title compound as a colourless oil (28 mg, 53%). ¹H-NMR; δ(CD₃OD), 8.29 (0.5H, s, CHO), 8.04-7.90 (1.5H, CHO and ArH), 7.50-7.20 (5H, m, ArH), 7.23-6.87 (3H, ArH), 4.90-4.60 (2H, br m, CH₂Ph), 4.25-3.95 (7H, m), 3.83 (3H, s, CH₃O), 2.18-1.95 (2H, m), 1.90-0.85 (11H, m). LRMS: +ve ion: 531 [M+23], 360.

Step B:

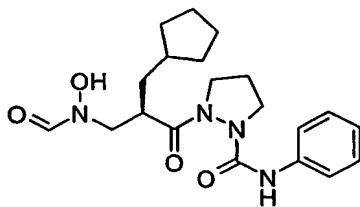
2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid (2-methoxyphenyl)amide

To a solution of the 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-carboxylic acid (2-methoxyphenyl)amide (28 mg, 0.055 mmol) in MeOH (2 ml) at rt under argon was added 10% Pd/C (3 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 1 h. After this time, the suspension was

filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (18 mg, 78%). ¹H-NMR; δ (CD₃OD), 8.20-7.65 (2H, br m, CHO and ArH), 7.23-6.87 (3H, m, ArH), 4.30-3.10 (7H, m), 3.85 (1.5H, s, CH₃O), 3.84 (1.5H, s, CH₃O), 2.15-2.00 (2H, m), 1.90-0.90 (11H, m). LRMS: +ve ion: 441 [M+23]. HPLC Rt = 5.12 min (214 nm).

The compounds of Example 39-42 were prepared by methods analogous to that of Example 38

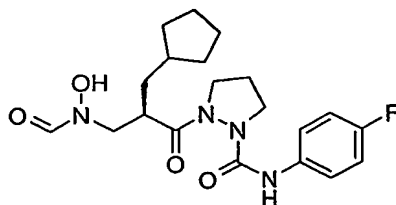
Example 39



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid phenylamide

LRMS: +ve ion: 411 [M+23]. HPLC Rt = 4.98 min (214 nm).

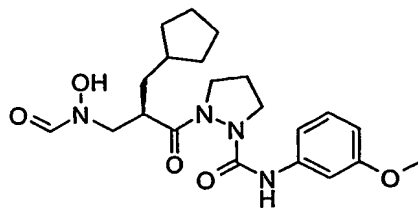
Example 40



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid (4-fluorophenyl)amide

LRMS: +ve ion: 429 [M+23]. HPLC Rt = 5.14 min (214 nm).

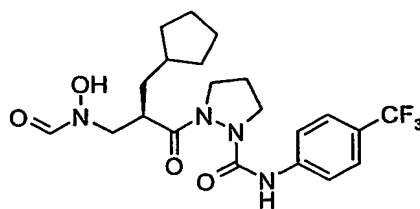
Example 41



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid (3-methoxyphenyl)amide

LRMS: +ve ion: 441 [M+23]. HPLC Rt = 5.04 min (214 nm).

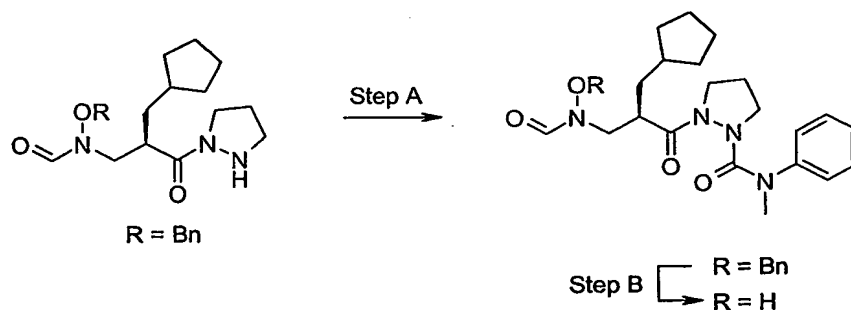
Example 42



2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid (4-trifluoromethylphenyl)amide

LRMS: +ve ion: 479 [M+23]. HPLC Rt = 5.68 min (214 nm).

Example 43



Step A. N-Methyl-N-phenyl carbamoyl chloride, MeCN, DIEA, reflux, 5 h; Step B. H₂ (g), 10% Pd/C, MeOH, rt, 2 h.

Step A:

2-[3-(Benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-

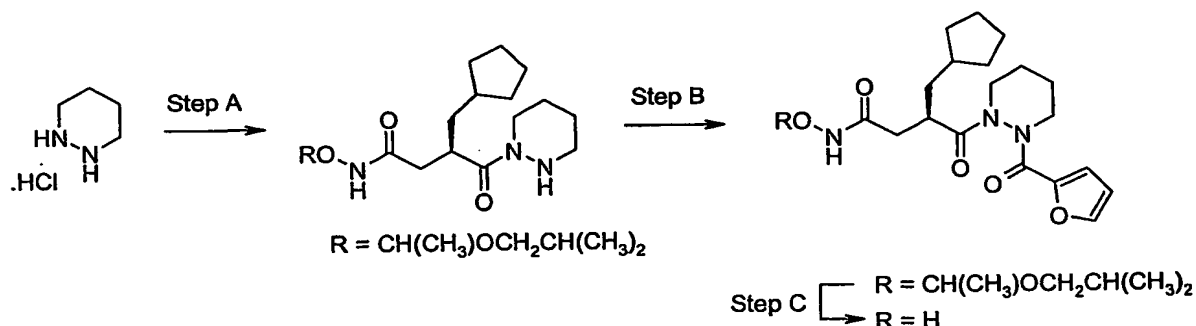
carboxylic acid methylphenylamide

To a solution of *N*-benzyloxy-*N*-[(2*R*)-cyclopentylmethyl-3-oxo-3-pyrazolidin-1-yl-propyl]formamide (72 mg, 0.20 mmol) in MeCN (3 ml) containing DIEA (42 μ l, 0.24 mmol) was added *N*-methyl-*N*-phenyl carbamoyl chloride (34 mg, 0.20 mmol). The reaction mixture was then heated to reflux where it was maintained for 5 h. After this time the mixture was concentrated under reduced pressure and purified by preparative HPLC. The title compound was isolated as a colourless solid (40 mg, 41%). LRMS: +ve ion: 515 [M+23], 386, 235.

Step B:**2-[(2*R*)-Cyclopentylmethyl-3-(formylhydroxyamino)-propionyl]-pyrazolidine-1-carboxylic acid methylphenylamide**

To a solution of 2-[3-(benzyloxyformylamino)-(2*R*)-cyclopentylmethyl-propionyl]-pyrazolidine-1-carboxylic acid methylphenylamide (40 mg, 0.08 mmol) in MeOH (4 ml) at rt under argon was added 10% Pd/C (4 mg). Hydrogen gas was bubbled through the black suspension for 15 min and then the reaction was left under an atmosphere of hydrogen for 2 h. After this time, the suspension was filtered and the collected solids were washed with additional MeOH. The combined filtrate and washings were concentrated under reduced pressure to give the title compound as a colourless solid (31 mg, 95%). ¹H-NMR; δ (CD₃OD), 8.31 (0.25H, s, CHO), 8.15 (0.25H, s, CHO), 7.97 (0.25H, s, CHO), 7.80 (0.25H, s, CHO), 7.50-7.28 (5H, m, ArH), 4.00-2.60 (7H, m), 3.37 (0.75H, s, NMe), 3.34 (0.75H, s, NMe), 3.31 (1.5H, s, NMe), 2.05-1.35 (11H, m), 1.25-0.95 (2H, m). LRMS: +ve ion: 425 [M+23], 296, 235, 206. HPLC Rt = 4.98 min (214 nm).

Example 44



Step A. (2*R*)-Cyclopentylmethyl-N-(1-isobutoxyethoxy)-succinamic acid, EDAC, HOAt, DMF, 0°C to rt, 16 h; Step B. 2-furoyl chloride, DIEA, CH₂Cl₂, rt, 1 h; Step C. HCl, MeOH, rt, 2 h.

Step A:

(3*R*)-Cyclopentylmethyl-N-(1-isobutoxyethoxy)-4-oxo-(tetrahydropyridazin-1-yl)-butyramide

To a solution of (2*R*)-cyclopentylmethyl-N-(1-isobutoxyethoxy)-succinamic acid (482 mg, 1.53 mmol) in CH₂Cl₂ (5 ml) at 0°C under argon was added EDAC (323 mg, 1.68 mmol), HOAt (42 mg, 0.306 mmol), 1,2-diazacyclohexane hydrochloride (187 mg, 1.53 mmol), followed by DIEA (586 µl, 3.37 mmol). The resulting solution was stirred at 0°C for 1 h and then warmed slowly to rt where it was maintained for 18 h. After this time the mixture was concentrated under reduced pressure and the crude residue was partitioned between EtOAc and sat. NaHCO₃. The aqueous phase was removed and extracted with additional EtOAc (x2). The combined organic fractions were dried (MgSO₄), filtered and concentrated under reduced pressure to give a pale yellow oil. This oil was purified by chromatography on silica eluting with 100% EtOAc to provide the title compound as a colourless oil (136 mg, 23%). LRMS: +ve ion: 406 [M+23], 384 [M+1]. ¹H-NMR; δ(CDCl₃), 8.53 (0.5H, br s, NH), 8.40 (0.5H, br s, NH), 4.95-4.87 (1H, m, OCHO), 4.02-3.15 (6H, m), 3.10-2.80 (2H, m), 2.55-2.20 (1H, m), 1.90-1.30 (15H, m), 1.36 (1.5H, d, J = 5Hz, CH₃CH), 1.35 (1.5H, d, J = 5Hz, CH₃CH), 1.20-1.00 (2H, m), 0.92 (6H, d, J = 6.5Hz).

Step B:

(3*R*)-Cyclopentylmethyl-4-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-N-(1-isobutoxyethoxy)-4-oxo-butyramide

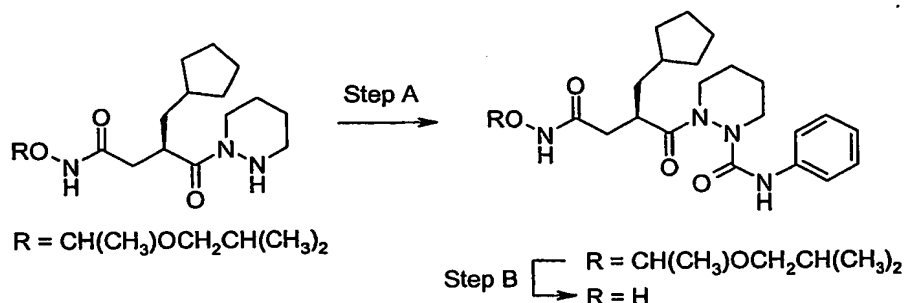
To a solution of (3*R*)-cyclopentylmethyl-N-(1-isobutoxyethoxy)-4-oxo-(tetrahydropyridazin-1-yl)-butyramide (65 mg, 0.17 mmol) in CH₂Cl₂ (2 ml) containing DIEA (32 μ l, 0.19 mmol) at rt under argon was added 2-furoyl chloride (22 mg, 0.17 mmol). The reaction mixture was stirred for 1 h at rt and then washed with 1M citric acid, 1M Na₂CO₃ and sat. NaCl. The organic layer was dried (MgSO₄), filtered and concentrated under reduced pressure to give a colourless foam. The crude product was used without further purification (74 mg, 91%). LRMS: +ve ion: 500 [M+23], 478 [M+1], 404.

Step C:

(3*R*)-Cyclopentylmethyl-4-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-N-hydroxy-4-oxo-butyramide

To a solution of (3*R*)-cyclopentylmethyl-4-[2-(furan-2-carbonyl)-tetrahydropyridazin-1-yl]-N-(1-isobutoxyethoxy)-4-oxo-butyramide (74 mg, 0.16 mmol) in MeOH (2 ml) at rt in air was added aq. HCl (171 μ l of a 1M solution, 0.17 mmol). The resulting solution was stirred for 2 h at rt. After this time the reaction was concentrated under reduced pressure and the crude product was purified by preparative HPLC to give the title compound as a colourless solid (32 mg, 55 %). ¹H-NMR; δ (CH₃OD), 7.80-7.60 (1 H, m, HetArH), 7.20-7.05 (1H, br m, HetArH), 6.67-6.50 (1H, br m, HetArH), 4.70-4.30 (2H, br m), 3.60-3.40 (1H, br m), 3.40-2.80 (2H, br m), 2.52-2.28 (2H, m), 1.90-0.70 (15H, br m). LRMS: +ve ion: 400 [M+23], 378 [M+1], 345, 181. HPLC Rt = 4.75 min (214 nm).

Example 45



Step A. 3,5-Bis-(trifluoromethyl)phenyl isocyanate, EtOAc, rt, 16 h; Step B. HCl, MeOH, rt, 4 h.

Step A:

2-[(2*R*)-Cyclopentylmethyl-3-(1-isobutoxyethoxycarbonyl)-propionyl]-tetrahydropyridazine-1-carboxylic acid phenylamide

To a solution of (3*R*)-cyclopentylmethyl-N-(1-isobutoxyethoxy)-4-oxo-(tetrahydropyridazin-1-yl)-butyramide (65 mg, 0.17 mmol) in EtOAc (2 ml) at rt under argon was added phenyl isocyanate (20 mg, 0.17 mmol). The resulting mixture was stirred for 16 h at rt and then concentrated under reduced pressure to give a colourless foam. The crude product was used without further purification (assumed quantitative yield, 0.17 mmol). LRMS: +ve ion: 525 [M+23], 503 [M+1], 370, 310, 251.

Step B:

2-[(2*R*)-Cyclopentylmethyl-3-hydroxycarbonylpropionyl]-tetrahydropyridazine-1-carboxylic acid phenylamide

To a solution of 2-[(2*R*)-cyclopentylmethyl-3-(1-isobutoxyethoxycarbonyl)-propionyl]-tetrahydropyridazine-1-carboxylic acid phenylamide (0.17 mmol) in MeOH (2 ml) at rt in air was added aq. HCl (187 μ l of a 1M solution, 0.19 mmol). The resulting solution was stirred for 4 h at rt. After this time the reaction was concentrated under reduced pressure and the crude product was purified by preparative HPLC to give the title compound as a colourless solid (30 mg, 44 %).

¹H-NMR; δ (CH₃OD), 7.67-7.57 (1H, m, ArH), 7.47-7.44 (1H, m, ArH), 7.32-7.24 (2H, m, ArH), 7.11-6.99 (1H, m, ArH), 4.60-4.30 (2H, br m), 4.90-2.30 (5H, m), 1.90-0.90

(15H, m). LRMS: +ve ion: 400 [M+23], 378 [M+1], 345, 181. HPLC Rt = 5.15-5.46 min [rotamers] (214 nm).

Biological Example

Minimal Inhibitory concentrations (MIC) of inhibitors against clinical isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* obtained from the Public Health and Clinical Microbiology Laboratory, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QW, UK, were determined by a standard agar plate dilution method following recommendations in **British Society for Antimicrobial Chemotherapy Working Party**. 1991. "A guide to sensitivity testing British Society for Antimicrobial Chemotherapy, London, United Kingdom". Briefly Iso-Sensitest agar (pH 7.2: Oxoid, United Kingdom) was employed supplemented with 5% horse blood (Oxoid) and 20 µg of NAD (Sigma) per ml to support growth of fastidious bacteria. The inoculum used was approximately 10^4 colony forming units of each isolate contained in a volume of 1 µl. Plates were incubated 18 to 24 hr in air, or for fastidious bacteria an atmosphere enriched with 4-6% carbon dioxide at 35°C. The MIC was determined as the lowest concentration of an antimicrobial tested that inhibited growth of the inoculum, disregarding a single persisting colony or faint haze caused by the inoculation.

The compounds of the Examples were are antibacterially active in the above assays, The following table states the MICs or MIC ranges of the tested compounds against 6 strains of *S. pneumoniae*, 4 strains of *H. influenzae* and 3 strains of *M. catarrhalis*.

Example	<i>S.pneumoniae</i> µg/ml	<i>H. Influenzae</i> µg/ml	<i>M. catarrhalis</i> µg/ml
1	0.5-2	<0.125-0.25	<0.125
2	1-8	0.25-8	0.25
3	0.5-2	1-4	0.125
4	0.5-4	16->32	0.5
5	2-16	208	0.25
6	0.5-2	4-8	0.06

7	0.5-4	1->32	0.5
8	0.5-4	1-8	0.5
9	0.5-2	0.125-8	<0.93
10	0.5-4	0.5-2	0.5
11	0.5-4	0.25-2	0.25
12	2-16	16-32	1
13	8-16	8->16	2
14	2-4	<0.125-4	<0.125
15	2-4	<0.125-4	<0.125
16	4-8	<0.125-4	<0.125
17	4-8	0.125	<0.125
18	4	0.25-16	<0.125
19	2-4	<0.125-4	<0.125
20	4-8	0.5-2	<0.03
21	1-4	4-16	0.125
22	4-16	8->16	2
23	8-16	0.5-2	<0.125
24	4-16	1-4	<0.125
25	4-8	<0.125-1	<0.125
26	8	1-8	0.125
27	16	2-16	0.06
28	0.5-4	16	0.06
29	4-8	2-16	0.06
30	16-32	2->32	0.125
31	8	4-16	0.06
32	1-8	16	0.25
33	4-16	16-32	0.06
34	8-16	4-16	0.125
35	16	4-8	0.125
36	8	2-32	0.125
37	4	1->32	0.06
38	8-16	1-2	0.25
39	4-16	<0.125-2	<0.125
40	8-16	<0.125-2	<0.125
41	4-8	<0.125-2	<0.125
42	2-8	2-8	Not tested

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43	8->32	16-32	8
44	2-4	0.06-0.125	0.6
45	4-8	1-4	Not Tested